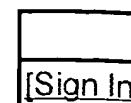




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## **A ligand-gated association between cytoplasmic domains of UNC5 and DCC family receptors converts netrin-induced growth cone attraction to repulsion.**

**Hong K, Hinck L, Nishiyama M, Poo MM, Tessier-Lavigne M, Stein E.**

Department of Biology, University of California, San Diego 92093, USA.

Netrins are bifunctional: they attract some axons and repel others. Netrin receptors of the Deleted in Colorectal Cancer (DCC) family are implicated in attraction and those of the UNC5 family in repulsion, but genetic evidence also suggests involvement of the DCC protein UNC-40 in some cases of repulsion. To test whether these proteins form a receptor complex for repulsion, we studied the attractive responses of Xenopus spinal axons to netrin-1, which are mediated by DCC. We show that attraction is converted to repulsion by expression of UNC5 proteins in these cells, that this repulsion requires DCC function, that the UNC5 cytoplasmic domain is sufficient to effect the conversion, and that repulsion can be initiated

netrin-1 binding to either UNC5 or DCC. The isolated cytoplasmic domains of DCC and UNC5 proteins interact directly, but this interaction is repressed in the context of full-length proteins. We provide evidence that netrin-1 triggers the formation of a receptor complex of DCC and UNC5 proteins and simultaneously derepresses the interaction between the cytoplasmic domains, thereby converting DCC-mediated attraction to UNC5/DCC-mediated repulsion.

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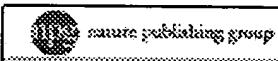
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**Llambi F, Causeret F, Bloch-Gallego E, Mehlen P.**

Apoptosis/Differentiation Laboratory-label La Ligue, Mo and Cellular Genetic Center, CNRS UMR 5534, Universi Lyon, 69622 Villeurbanne, France.

The membrane receptors DCC and UNC5H have been shown to be crucial for axon guidance and neuronal migration by acting as receptors for netrin-1. DCC has also been proposed as a dependence receptor inducing apoptosis in cells that are dependent on netrin-1 availability. Here we show that the netrin-1 receptors UNC5H (UNC5H1, UNC5H2, UNC5H3) also act as dependence receptors. UNC5H receptors induce apoptosis; this effect is blocked in the presence of netrin-1. Moreover, we demonstrate that UNC5H receptors are cleaved in vitro by caspase 3 in their intracellular domains. This cleavage may expose the exposure of a fragment encompassing a death domain required for cell death induction in vivo. Finally, we present evidence that during development of the nervous system, the presence of netrin-1 is crucial to maintain survival of UNC5H and DCC-expressing neurons, especially in the ventricles of the brainstem. Altogether, these results argue for a role

netrin-1 during the development of the nervous system, not only as a guidance cue but as a survival factor via its receptors and UNC5H.

PMID: 11387206 [PubMed - indexed for MEDLINE]

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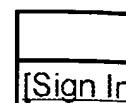
Max Planck Institute for Brain Research, Deutschordensstr 46, 60528 Frankfurt, Germany. d.engelkamp@mpih-frankfurt.mpg.de

The *Caenorhabditis elegans* gene *unc-5* and its vertebrate homologues are Netrin receptors. In this study, I report the cloning of three mouse Unc5 family members, namely, Unc5h1, Unc5h2 and Unc5h4. Furthermore, a comparative expression analysis is presented with Unc5h3, deleted in colorectal cancer and Netrin-1. Transcript distribution is studied during early development, mammary bud formation, vascularisation, a limb development. The most widely expressed Unc5 family member is Unc5h2 and its mRNA is observed during early blood vessel formation, in the semicircular canal and in a dorsal to ventral gradient in the retina. Unc5h1 expression is restricted to the central nervous system, whereas, sites of Unc5h4 expression are in the developing limb and mammary gland.

PMID: 12351186 [PubMed - indexed for MEDLINE]



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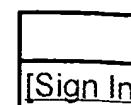
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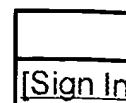
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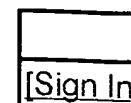
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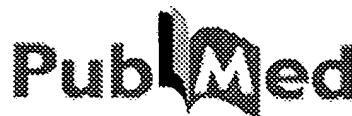
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## Guidance of developing axons by netrin-1 and its receptors.

**Leonardo ED, Hinck L, Masu M, Keino-Masu K, Faze Stoeckli ET, Ackerman SL, Weinberg RA, Tessier-Lavigne M.**

Howard Hughes Medical Institute, Department of Anatomy and Cell Biology, University of California, San Francisco 94143, USA.

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## Vertebrate homologues of *C. elegans* UNC-5 are candidate netrin receptors.

Leonardo ED, Hinck L, Masu M, Keino-Masu K, Ackerson SL, Tessier-Lavigne M.

Howard Hughes Medical Institute, Department of Anatomy and Programs in Cell and Developmental Biology and Neuroscience, University of California, San Francisco 94152, USA.

In the developing nervous system, migrating cells and axons are guided to their targets by cues in the extracellular environment. The netrins are a family of phylogenetically conserved guidance cues that can function as diffusible attractants and repellents for different classes of cells and axons. In vertebrates, insects and nematodes, members of the DCC subfamily of the immunoglobulin superfamily have been implicated as receptors that are involved in migration towards netrin sources. The mechanisms that direct migration away from netrin sources (presumed repulsions) are less well understood. In *Caenorhabditis elegans*, the transmembrane protein UNC-4 (UNC-14) has been implicated in these responses, as loss of unc-4 function causes migration defects and ectopic expression of unc-5 in some neurons can redirect their axons away from netrin source. Whether UNC-5 is a netrin receptor or simply a

accessory to such a receptor has not, however, been defined. We now report the identification of two vertebrate homologues of UNC-5 which, with UNC-5 and the product of the mouse cerebellar malformation gene (rcm), define a new subfamily of the immunoglobulin superfamily, and whose messenger RNAs show prominent expression in various classes of different neurons. We provide evidence that these two UNC-5 homologues, as well as the rcm gene product, are netrin-b proteins, supporting the hypothesis that UNC-5 and its relatives are netrin receptors.

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